REMARKS

Claims 1-16 were pending. Claims 17 and 18 are added herein and no claims are canceled. Thus, upon entry of this amendment, **claims 1-18 will be pending**. Of these, claims 5-12 are currently withdrawn.

Claim 1 is amended to recite particular routes of administration for sodium nitrite and specify that administration results in contact of the sodium nitrite with blood in the subject, support for which can be found throughout the original application. For instance, support for specific routes of administration can be found, for example, on page 15, lines 37-39, and page 17, lines 10-14. Claim 1 is further amended to specify that non-acidified sodium nitrite is administered in a therapeutically effective amount to a subject to decrease blood pressure and/or increase vasodilation, support for which can be found throughout the application as filed.

Claim 16 is amended to replace "less than about 25 μM" with "no more than about 25 μM." New claims 17 and 18 specify that the circulating concentration is no more than about 20 μM or no more than about 16 μM, respectively. Support for amended claim 16 and new claims 17 and 18 can be found, for example, at page 12, lines 30-32; page 18, lines 36-38; and page 22, lines 31-32. No new matter is introduced by these amendments.

SUMMARY OF EXAMINER INTERVIEW

Applicants thank Examiners Pagonakis and Fetterolf for the courtesy of a telephone interview with Applicants' representatives Tanya M. Harding and Jodi L. Connolly on March 3, 2010. During the interview, the pending rejections under 35 U.S.C. § 102(b) and § 103(a) were discussed. The priority date of the pending claims was also discussed. Applicants' representatives proposed amending the claims to incorporate specific routes of administration (such as injection and inhalation) that were not taught in Shaw *et al.* The Examiners indicated that this should be sufficient to overcome the novelty rejection in view of Shaw *et al.*

Applicants' representatives also questioned the Examiners regarding the extent to which the five Declarations under 37 C.F.R. § 1.132, submitted with the prior response, were considered when setting forth the current rejection under 35 U.S.C. § 103(a), particularly in regard to the teachings of the Modin *et al.* reference. Applicants' representatives stated that it did not appear that the statements made in the Declarations were addressed in the current Office action. The Examiners requested that when responding to the current Office action, Applicants

point to specific statements in the Declarations that were not addressed, which Applicants have done below in response to the obviousness rejection.

In regard to the priority date of the current claims, Applicants' representatives stated that since this application is a U.S. National Stage application and the corresponding PCT application had sufficient support for *non-acidified* sodium nitrite, the claims are entitled to a priority date at least as of the PCT filing date, July 9, 2004. The Examiners requested that Applicants specifically point out support in the application for "non-acidified" sodium nitrite, which Applicants have done in this response.

Finally, Applicants' representatives requested that a subsequent telephone interview be granted after filing the current response and prior issuance of the next Office action. The Examiners agreed to such an interview.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 1 and 16 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office does not address how claim 1 lacks compliance with the written description requirement, therefore Applicants understand this rejection applies only to claim 16. The Office alleges that claim 16 lacks descriptive support for the phrase "less than about 25 μM." Applicants traverse this rejection.

As set forth in the Response After Final Action submitted on October 13, 2009, Applicants maintain that claim 16 is fully and adequately supported by the original specification. However, solely in an effort to advance prosecution of this application, claim 16 is amended to replace "less than about 25 μM" with "no more than about 25 μM."

As stated in the prior response, *in haec verba* written support is not necessary for a limitation, rather "an explicit or implicit suggestion by the disclosure" is sufficient. As amended herein, claim 16 specifies that the concentration of non-acidified nitrite in the circulating blood is no more than about 25 μM. The phrase "no more than about 25 μM" is supported at least implicitly by Applicants' disclosure. For instance, on page 12, lines 30-34, the specification indicates that "pharmaceutically-acceptable salts of nitrite (such as sodium nitrite) are effective as vasodilators at calculated dosages of about 0.6 to about 200 μM final concentration in the circulating blood of a subject." Similarly, on page 19, lines 8-9, the specification recites that "[i]n certain examples, the sodium nitrite is administered to a circulating concentration of about

0.6 to 240 μM." Additionally, the examples describe administration of non-acidified sodium nitrite to subjects to a concentration in the circulating blood of up to at least 221.82 μM (see page 39, line 36). See also Figure 13D and the accompanying text (*e.g.*, Example 3), which tracks plasma nitrite after inhalation of non-acidified sodium nitrite; the level is between about 30 μM and 15 μM. Moreover, page 18, lines 36-38 of the specification states that "in various embodiments the pharmaceutically-acceptable salt of nitrite is administered to a circulating concentration in the subject of no more than about 100 μM; no more than about 50 μM; no more than about 20 μM; no more than about 16 μM; or less than about 16 μM." Thus, implicit support is clearly present in the specification for circulating levels of non-acidified sodium nitrite at least at any level between 0.6 μM and 221.82 μM, with representative specific examples throughout this range.

Accordingly, the recitation of "no more than about 25 μM" is adequately supported by the application. In addition, new claims 17 and 18 find specific support in the specification, such as at page 18, lines 36-38. Thus, Applicants request withdrawal of this rejection under 35 U.S.C. § 112, first paragraph.

PRIORITY

The Office alleges that all of the pending claims are only entitled to a priority date of October 4, 2006, the "filing" date of the instant application. It is Applicants' understanding that this determination was based on the allegation that the priority provisional application and equivalent International Phase (PCT) of the current U.S. National Phase application do not provide support for *non-acidified* nitrite. Applicants strongly disagree.

The summary of the disclosure states that "nitrite does not need to be applied in an acidified condition in order for it to be effective in regulating the cardiovascular system, and more particularly to act as a vasodilator *in vivo*" (see page 2, line 39 to page 3, line 2), and further recites that the disclosed treatment methods can include administration of "non-acidified nitrite salt" (see page 4, lines 5-12). Similarly, page 14, lines 21-23 of the application repeat that sodium nitrite need not be acidified. Because this application is the U.S. National Stage of PCT/US2004/22232, filed July 9, 2004, and therefore contains the identical disclosure as the PCT application, the claims should be entitled to a priority date at least as of July 9, 2004.

The two provisional applications to which the current application claims benefit also disclose non-acidified sodium nitrite. For example, U.S. Application No. 60/485,959, filed July 9, 2003, states "The vasodilatory property of nitrite during basal blood flow conditions, when tissue pO_2 and pH are not exceedingly low, was surprising and unexpected" (see page 9, lines 20-21). Similarly, U.S. Application No. 60/511,244, filed October 14, 2003, states "The vasodilatory property of nitrite during basal blood flow conditions, when tissue pO_2 and pH are not exceedingly low, was unexpected" (see page 20, lines 1-2). In addition, these priority provisional applications discuss using pharmaceutical formulations that include water and physiologically acceptable buffered saline solutions, such as phosphate buffered saline solutions at a pH of about 7.0-8.0 (see page 14, 30-31 of US 60/511,244), and nitrite solutions of pH 7.0-7.4 for administration to subjects (see page 17, lines 9-11 of US 60/485,959). Thus, because both of the provisional applications teach the use of *non-acidified* sodium nitrite, Applicants submit that the pending claims are entitled to a priority date of July 9, 2003.

Applicants request that that Office acknowledge the earlier priority date of all of the pending claims, and the priority date of *at least as early as* July 9, 2004 for all of the pending claims, in the next Office communication.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 1-4 and 13-16 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The Office alleges that the term "non-acidified" is not defined in the application, therefore it is not clear what the term encompasses. Applicants traverse this rejection.

Applicants submit that it is clear from the description provided in the specification what is encompassed by the term "non-acidified" in relation to sodium nitrite. In particular, the specification teaches that sodium nitrite need not be "applied in an acidified condition" (see page 2, line 39 to page 3, line 2; and page 14, lines 21-23 of the specification). Thus, it is clear from the specification that "non-acidified" sodium nitrite refers to sodium nitrite that is not in an acidic solution. Accordingly, one of ordinary skill in the art would recognize that "non-acidified sodium nitrite" includes sodium nitrite at neutral or basic pH.

REJECTION UNDER 35 U.S.C. § 102

Claims 1, 2 and 13 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Shaw *et al.* (U.S. Patent No. 4, 650,484). The Office alleges that Shaw *et al.* teach treatment of ischemic conditions by administration of a therapeutically effective amount of a vasodilator (such as sodium nitrite) internally and transdermally (such as by buccal administration).

Although not in agreement with the Office's position, solely in an effort to advance prosecution of this application, claim 1 is amended herein to recite particular routes of administration (intravenous, intramuscular, rectal, *ex vivo*, intraocular, intraperitoneal, intraarterial, subcutaneous, inhalation, or into a cardiopulmonary bypass circuit), which are not taught in Shaw *et al.* Claims 2 and 13 depend from and therefore incorporate all limitations of claim 1. Accordingly, claims 1, 2 and 13 are not anticipated by Shaw *et al.* and Applicants request withdrawal of this rejection under 35 U.S.C. § 102(b).

REJECTION UNDER 35 U.S.C. § 103

Claims 1-4 and 13-16 are rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Shaw *et al.* and Modin *et al.* (*Acta. Physiol. Scand.* 171:9-16, 2001). The Office's summary of the alleged teachings of Shaw *et al.* are described above. The Office acknowledges that Shaw *et al.* do not teach a circulating concentration of 0.6 to 240 μM. However, the Office alleges that Modin *et al.* suggest how much sodium nitrite would be beneficial for treating an ischemic condition. The Office therefore concludes that it would have been *prima facie* obvious to use sodium nitrite at the concentrations cited in the pending claims. Applicants traverse this rejection.

The Office has failed to establish a *prima facie* case of obviousness

Applicants submit that the combination of cited art does not teach each and every element of the pending claims. Thus, the Office has failed to establish a *prima facie* case of obviousness against the claims. Neither Shaw *et al.* nor Modin *et al.* teach or even suggest that *non-acidified* nitrite is a vasodilator *in vivo*, or more particularly, that administration of non-acidified sodium nitrite decreases blood pressure and/or increases vasodilation in a subject. In addition, neither reference teaches or suggests administration of non-acidified sodium nitrite by a route selected from intravenous, intramuscular, rectal, *ex vivo*, intraocular, intraperitoneal, intraarterial,

subcutaneous, inhalation, and into a cardiopulmonary bypass circuit, as currently recited in the claims. Shaw *et al.* teach only administration by oral, sublingual and buccal routes (see column 5, line 12) and Modin *et al.* provide no teachings related to routes of administration as the studies described in Modin *et al.* are performed exclusively *in vitro*.

Moreover, the combination of cited references does not teach or suggest *a therapeutically effective amount* of non-acidified nitrite salt to decrease blood pressure and/or increase vasodilation in a subject. In addition, the combination of cited references does not teach or suggest administering non-acidified nitrite to achieve a circulating concentration of 0.6 to 240 μM, as recited in claim 4. Although Shaw *et al.* lists sodium nitrite as a potential vasodilator, this references provides no guidance on what a therapeutically effective amount of sodium nitrite would be to increase vasodilation or decrease blood pressure, as presently claimed. The Office alleges that Modin *et al.* cure this deficiency by teaching that human plasma has 0.45 μM nitrite and human serum has 6.6 μM nitrite. The Office concludes based on the teachings of Modin *et al.* that it would have been obvious to administer nitrite in an amount that would increase the plasma and serum concentrations of nitrite and that it would have been merely routine to optimize the amount of nitrite administered to a subject. However, Applicants point out that one of ordinary skill in the art reading Modin *et al.* would not have had any motivation to optimize *non-acidified* nitrite to decrease blood pressure and/or increase vasodilation because Modin *et al.* clearly teaches that acidified nitrite is a significantly better vasodilator. Furthermore, as discussed in more detail below, Modin *et al.* use an *in vitro* system that is not representative of the *in vivo* effects that occur in the presence of circulating blood. Thus, the dose used by Modin *et al.* in their *in vitro* system does not provide adequate guidance on an appropriate, therapeutically effective dose of non-acidified nitrite to administer to a subject. With particular regard to claims 4 and 16, the combination of cited references provides no teaching or suggestion of the specific doses or dosing regimens disclosed and claimed by Applicants.

In summary, the combination of cited references does not teach that *non-acidified* nitrite is a vasodilator *in vivo* and further does not teach *a therapeutically effective amount* of *non-acidified* nitrite to administer to a subject in order to decrease blood pressure and/or increase vasodilation, particularly by any one of the routes recited in the pending claims. Accordingly, the Office has failed to establish a *prima facie* case of obviousness.

Declarations under 37 C.F.R. § 1.132

Included with the Response After Final Action submitted by Applicants on October 13, 2009 were five Declarations under 37 C.F.R. § 1.132 (the King, Ignarro, Freeman, Kelm and Lundberg Declarations), which detailed differences between the present application and the cited art. During the telephone interview of March 3, 2010, Applicants' representatives stated that the current Office action did not appear to address several important points raised in the Declarations. The Examiners requested that in the current response, Applicants note specific points discussed in the Declarations that were overlooked. In accordance with this request, Applicants have specifically addressed several important points from the Ignarro, Kelm and Lundberg Declarations below. For the sake of brevity, Applicants have not reiterated everything discussed in the Response of October 13, 2009; however, Applicants maintain that the arguments presented in the prior response as they relate to Modin *et al.* are still relevant to the current obviousness rejection.

First, page 10 of the current Office action refers to the Kelm and Lundberg Declarations, which state that the aortic ring assay of Modin *et al.* is not representative of *in vivo* function. The Office interprets the Kelm Declaration as stating that the Modin *et al.* system is a poor model because the excised aorta is maintained at neutral or acidified pH. However, Applicants respectfully point out that this is not what Dr. Kelm asserts in the Declaration and the Office has missed the primary issue regarding this assay, which is clearly laid out in each of the Kelm, Lundberg and Ignarro Declarations. The problem with the aortic ring bioassays disclosed by Modin *et al.* does not relate to the pH at which the experiments are performed, but rather the fact that the assay is performed in the absence of blood (in contrast to Applicants' currently claimed invention). Paragraph 4 of the Kelm Declaration, paragraph 5 of the Ignarro Declaration and paragraph 3 of the Lundberg Declaration specifically discuss this issue. In particular, the Kelm Declaration states that the model used by Modin *et al.* is a poor model because "the regulatory factors present in blood that play a physiological role in the vasodilation process are absent...*Of particular importance is the lack of blood in the aortic ring preparations.*" It should be noted that Dr. Lundberg was the senior author of the Modin *et al.* paper and he asserts that because the published assays were performed in the absence of blood, the findings "were not considered predictive of whether or not similar concentrations of inorganic nitrite would cause vasodilation under non-acidic/non-hypoxic physiological conditions *in vivo*" (see paragraph 3 of the

Lundberg Declaration). Thus, even the senior author of the Modin *et al.* manuscript does not believe his own earlier study (Modin *et al.*) was predictive of Applicants' presently claimed subject matter.

Second, the Kelm, Lundberg and Ignarro Declarations state that in spite of Modin *et al.*, scientists working in the nitrite field prior to Applicants' invention would not have believed that non-acidified organic nitrite at physiologic concentrations was a vasodilator *in vitro* or *in vivo* (see paragraphs 6-8 of the Ignarro Declaration, paragraph 4 of the Lundberg Declaration and paragraphs 6-8 of the Kelm Declaration). In particular, each of the Declarations references the Lauer *et al.* paper (of which Dr. Kelm is the senior author), which demonstrates that physiological concentrations of nitrite do not cause vasodilation and specifically shows that no vasodilation occurs *in vivo* at venous plasma nitrite concentrations of 130 μM. Dr. Kelm specifically states that his research group held a "strong belief, based on our research studies and those of others in the field, that plasma nitrite had no physiological effect on vasodilation" (see paragraph 6 of the Kelm Declaration). Dr. Kelm further indicates in the same paragraph that he believes that his group's research studies (that is, Lauer *et al.*) were widely accepted by the scientific community. Dr. Ignarro, the PNAS editor that reviewed and edited the Lauer *et al.* paper, concurred with this belief. It should be noted that Dr. Ignarro is a Nobel Laureate that received the Nobel Prize for his work in the field of nitric oxide and its effects on the cardiovascular system. Dr. Ignarro asserts that because the Lauer *et al.* paper was published in PNAS, scientists working in the field were likely to read and trust the results (see paragraph 7 of the Ignarro Declaration).

Third, both the Lundberg and Kelm Declarations point out that the results disclosed by the inventors in their manuscript (Cosby *et al.*, *Nature Med.* 9(12):1498-1505, 2003) were surprising to most scientists working in the field at the time because of the overwhelming evidence from prior studies that nitrite was not an *in vivo* vasodilator. In particular, Dr. Lundberg states that the Cosby *et al.* paper "was met with wide skepticism until the results were reproduced later by a number of other laboratories" (see paragraph 4 of the Lundberg Declaration). Thus, experts in the nitrite field believed the inventors' findings to be surprising and unexpected.

Applicants request that each of the Declarations submitted with the October 13, 2009 response be considered in detail, particularly the points discussed above, which are specifically addressed by the Kelm, Lundberg and Ignarro Declarations.

The claimed methods would not have been predictable to one of ordinary skill in the art

Applicants further submit that there could have been no predictable or reasonable expectation that one of ordinary skill in the art could have reached Applicants' invention based on the teachings of the cited references and in view of the prior art as a whole. Shaw *et al.* and Modin *et al.* fail to satisfy the requirements for a finding of obviousness of the pending claims in accordance with the requirements of the "Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*" (72 Fed. Reg. 57526-57535, October 10, 2007) (the "Guidelines").

The Guidelines provide the following non-exclusive rationales for supporting a finding that a claimed invention is obvious (emphasis added), which rationales have subsequently been incorporated in the M.P.E.P. at § 2143:

(A) combining prior art elements according to known methods to yield **predictable** results;

(B) simple substitution of one known element for another to obtain **predictable** results;

(C) use of known technique to improve similar devices (methods, or products) in the same way;

(D) applying a known technique to a known device (method, or product) ready for improvement to yield **predictable** results;

(E) "obvious to try" - choosing from a finite number of identified, **predictable** solutions, **with a reasonable expectation of success;**

(F) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been **predictable** to one of ordinary skill in the art; and

(G) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

The emphasis in the Guidelines is accordingly the **predictability** of the combination of elements from the prior art, as a basis for a finding that there is a reasonable expectation of success associated with a prior art combination. It is respectfully submitted that in the present case, there is **no such element of predictability in the purported combination of art references, and accordingly no reasonable expectation of success**. Thus, the obviousness rejections cannot stand.

One significant difference between the claimed subject matter and the teachings of the cited art is that the studies of Modin *et al.* were conducted in aortic ring bioassays **without circulating blood**, in contrast to Applicants' methods.[1] The Modin *et al.* studies are qualitatively not different from similar work performed by Robert Furchgott in 1952 (Furchgott & Bhadrakom, *J. Pharmacol. Exp. Ther.* 108(2):129-43, 1953; of record). These experiments were all performed in **isolated** aortic rings **without blood in them**. Because these studies required non-physiological conditions – extremely low oxygen tension and low pH, as well as high nitrite concentrations – they were not considered by those of skill in the art to reflect what would happen in the human circulation (that is, in the presence of blood).

Thus, there would be no reasonable expectation that sodium nitrite as employed in Modin *et al.* would predictably function in the methods provided in Shaw *et al.* – that is, there was no reasonable expectation that sodium nitrite would work *in vivo* in the presence of blood. This was clearly evinced by the Lauer *et al.* paper (*Proc. Natl. Acad. Sci. USA* 98:12814-12819, 2001; of record)) – which concluded that "nitrite lacks intrinsic vasodilator action." One of skill in the art, prior to Applicants' invention, would have expected that the presence of blood would have **inhibited** the NO generated from nitrite, not increased it.

It was shown by Isbell *et al.* (*Am. J. Physiol. Heart Circ. Physiol.* 293(4):H2565-72, 2007; of record) that oxygenated blood inhibits the nitrite induced vasodilation of aortic rings. Thus, it is very clear that the results of *in vitro*, blood-free experiments such as described in Modin *et al.* **are not applicable to an *in vivo* situation**.

The Office alleges on page 10 of the Office action (bottom paragraph) that Applicants' argument that the aortic ring bioassays are not predictive of an *in vivo* setting are not persuasive because Pawloski *et al.* teach the use of aortic ring bioassays to examine the relationship between NO content and RCE vasoactivity and the authors conclude that "impaired hypoxic vasodilation

[1] This difference is further elaborated herein and in the Declarations submitted October 13, 2009

by RBCs *ex vivo* is a physiological correlate of vasoocclusion in vivo" (page 2536, column 1). Without conceding to the validity of this statement, Applicants point out that the Pawloski *et al.* reference was published after the priority date of the pending claims (see discussion above in regard to priority) and is therefore not a relevant teaching as to what one of skill in the art would have understood about aortic ring bioassays at the time of Applicants' disclosure.

In addition, the Modin *et al.* reference itself teaches away from Applicants' invention. As indicated in Section 2141.02 of the MPEP, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including those portions that would lead away from the claimed invention. (*W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984)). As discussed above, Modin *et al.* teach that acidified inorganic nitrite is preferred, and therefore that non-acidified inorganic nitrite is not preferred. The clear teaching of Modin *et al.* is that inorganic nitrite is a more effective vasodilator in an acidic environment as compared to a non-acidic environment. Thus, if one of ordinary skill in this art were to consult Modin *et al.* in relation to Shaw *et al.*, the only potentially reasonable conclusion to draw from Shaw *et al.* would be to use sodium nitrite in an acidic environment, as it is more efficient and effective.

Even if, for the sake of argument, the compound used by Modin *et al.* was deemed a reasonable substitute to the compound used by Shaw *et al.* (which Applicants do not admit), there is no credible support for an allegation that one of ordinary skill would have used the (allegedly) non-acidified sodium nitrite of Modin *et al.* in the method of Shaw *et al.* Modin *et al.* is more than a "mere disclosure of more than one alternative" (MPEP 2141.02), but instead is a clear teaching away that criticizes, discredits, or otherwise discourages the solution claimed by Applicant. See *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004).

It is respectfully submitted that in the present case, the Office has not demonstrated that one of ordinary skill in the art would have had a **predictable and reasonable expectation of success in combining the teachings of the cited references** to yield Applicants' invention. Thus, the pending claims are not obvious in view of the cited art.

Conclusion

For at least the reasons set forth above, and already of record in the application, Applicants assert that the pending claims are not obvious. Accordingly, withdrawal of this rejection under 35 U.S.C. § 103(a) is requested.

DOUBLE PATENTING REJECTION

Claims 1-4 and 13-15 are provisionally rejected on the ground of non-statutory obviousness-type double patenting over claims 1, 6-13 and 20-23 of co-pending Application No. 10/563,682. Applicants continue to request that this rejection be held in abeyance until claims from one or both of the applications have been allowed.

REQUEST FOR EXAMINER INTERVIEW AND CONCLUDING STATEMENT

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and allowance of the claims is respectfully requested. If any issues remain, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office Action in order to arrange a telephonic interview. It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request.

Respectfully submitted,

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